Current evidence for central analgesic effects of NSAIDs: an overview of the literature

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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for a variety of painful conditions. Their peripheral anti-inflammatory effect due to inhibition of prostaglandin synthesis is well documented. In the late 1980's, animal data suggested for the first time that NSAIDs might have central effects as well. Since that time, central inflammatory and nociceptive pathways that are potential targets of NSAIDs have been extensively studied in both animal and human models. This review provides an overview of the relevant literature implicated in the central effects of NSAIDs. The role of different enzymes and mediators, as well as the central effects of NSAIDs are discussed. Literature search was performed by PubMed NCBI. A large body of evidence supports the central effects of NSAIDs in animal models of inflammatory pain conditions. Relevant mechanisms that underlie this central action involve spinal upregulation of the enzyme cyclooxygenase, increased spinal prostaglandin E2 production, modulation of inhibitory fast synaptic currents in lamina I and II of the dorsal horn, and glycine-dependent modulation of pain. Results from animal models are not yet sufficiently supported by human studies. This does not necessarily imply that the central effects of NSAIDs are irrelevant to human pain, but rather that methodological and regulatory barriers are the limiting step to translating findings from animal studies to human research protocols.

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EXPERTS' OPINION

Current evidence for central analgesic effects of NSAIDs: an overview of the literature

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for a variety of painful conditions. Their peripheral anti-inflammatory effect due to inhibition of prostaglandin synthesis is well documented. In the late 1980's, animal data suggested for the first time that NSAIDs might have central effects as well. Since that time, central inflammatory and nociceptive pathways that are potential targets of NSAIDs have been extensively studied in both animal and human models. This review provides an overview of the relevant literature implicated in the central effects of NSAIDs. The role of different enzymes and mediators, as well as the central effects of NSAIDs are discussed. Literature search was performed by PubMed NCBI. A large body of evidence supports the central effects of NSAIDs in animal models of inflammatory pain conditions. Relevant mechanisms that underlie this central action involve spinal upregulation of the enzyme cyclooxygenase, increased spinal prostaglandin E_2 production, modulation of inhibitory fast synaptic currents in lamina I and II of the dorsal horn, and glycine-dependent modulation of pain. Results from animal models are not yet sufficiently supported by human studies. This does not necessarily imply that the central effects of NSAIDs are irrelevant to human pain, but rather that methodological and regulatory barriers are the limiting step to translating findings from animal studies to human research protocols.

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KEY WORDS: Non-steroidal anti-inflammatory agents - Prostaglandins - Cyclooxygenase 1 - Cyclooxygenase 2.

Worldwide, non-steroidal anti-inflammatory drugs (NSAIDs) are the backbone in first-line pain management.[1] Hereby NSAIDs analgesic efficacy has been mainly explained by their peripheral effect in the setting of an inflammatory response to injury. Tissue damage is associated with the release of inflammatory mediators, leading to sensitization of peripheral nociceptors and thus causing sustained pain and hypersensitivity. Inhibition of the cyclooxygenase 1 and 2 (COX-1 and COX-2) by NSAIDs reduces the inflammatory response by inhibiting prostaglandin synthesis, thereby alleviating pain. Coxibs, the COX-2 selective inhibitors, were designed to reduce gastrointestinal side effects associated with conventional NSAIDs. In the early 1990's, evidence suggested for the first time that NSAIDs might exert an effect in the central nervous system, as intrathecally administered NSAIDs were able to abolish hyperalgesia caused by spinal excitatory neurotransmitters.[2, 3] This review gives an overview of the most important experimental findings supporting a central mode of action of NSAIDs, starting with data from animal studies and linking them to possible mechanisms in humans.

Overview of mediators and mechanisms

Two isoenzymes of cyclooxygenase exist, COX-1 and COX-2, both of which are inhibited by traditional, *i.e.* nonselective, NSAIDs. Newer compounds called Coxibs selectively inhibit COX-2. COX-1 is constitutively expressed in peripheral tissues such as gastric mucosa, kidneys or blood platelets, whereas COX-2 is induced in various tissues during inflammatory processes. However, in the central nervous system, both isoforms are usually present.[4] Upon nociceptive stimulation, COX catalyzes the rate-limiting step in prostaglandin synthesis by forming PGH_2 from arachidonic acid. PGH_2 is subsequently transformed to various isoforms, such as PGD_2, PGE_2, PGF_2 and PGI_2 (prostacyclin). In terms of pain and nociception, PGE_2 is the most extensively studied. Prostaglandins exert their effects by binding to specific receptors DP, EP, FP and IP for PGD_2, PGE_2, PGF_2 and PGI_2, respectively. All of them are G-protein-coupled receptors that affect intracellular signaling by second messengers such as cAMP or inositol-triphosphate.[5] Four receptor subtypes for PGE_2 (EP1-EP4 receptors), with partially opposing signaling pathways, are responding to the naturally occurring agonist PGE_2.[6] They have been described by Coleman *et al.* in 1994.[7] Activation of EP1 receptors increase intracellular Ca^{2+}, while EP2 and EP4 lead to increased cAMP. Effects of EP3 receptors seem to be mediated by a decrease in cAMP.[8]

Spinal prostaglandins and COX inhibitors in animal models

Among the different prostanoids, prostaglandin E_2 (PGE_2) was revealed to be a main contributor to painful responses in inflammatory conditions.[9] As an example, intrathecal injection of PGE_2 causes dose-dependent hyperalgesia, whereas PGD_2, PGF_2 and PGI_2 have no such effect.[10, 11] Animal data revealed significant increases in spinal cord PGE_2 levels in various pain models, such as peripheral inflammation[12] and rat models of surgical[13] and neuropathic pain.[14] Whether this increase in PGE_2 is due to COX-1 or COX-2 seems to depend on the nature of the painful stimulus: while inflammatory pain (*e.g.* injection of formalin or complete Freund's adjuvant) seems to upregulate spinal COX-2,[15, 16] surgical pain by paw incision results in upregulation of spinal COX-1.[17] The link between spinal PGE_2 upregulation and pain could be confirmed experimentally in inflammatory pain models, whereby intrathecally administered inhibitors of COX-1 and COX-2 decreased spinal PGE_2 production with an associated decrease in central sensitization of pain.[11, 16, 18, 19] Insofar PGE_2-induced central sensitization seems to be mediated by a COX-2-PGE_2 response to proinflammatory cytokines,[20-22] resulting in phosphorylation and inhibition of the glycine receptor α3 in the superficial spinal cord dorsal horn[23, 24] (Figure 1). This was recently confirmed in a murine model of inflammatory pain, where 2,6-di-*tert*-buthylphenol reversed inflammation-mediated spinal nociception trough specific interaction with the phosphorylated glycine α3 receptors, thereby reducing hyperalgesia.[25]

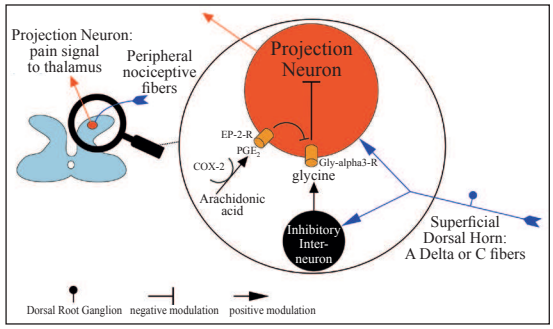

Figure 1.—Central effects of NSAIDs.
COX: cyclooxygenase; EP-2-R: EP2-receptor; PGE_2: prostaglandin E2; Gly-alpha3-R: glycine receptor α3.

Role of EP receptors in animal pain

The role of different EP receptor subtypes has been only partially clarified. Olivia *et al.* injected the non-selective prostaglandin agonist misoprostol into the periaqueductal grey (PAG) in mice. Subsequent application of specific agonists for EP1-4 receptor subtypes into the PAG all inhibited the central late phase of formalin-induced hyperalgesia.[26] Nakayama *et al.* applied PGE_2 intrathecally in rats and observed stable hyperalgesia associated with increased Ca^{2+} in the dorsal horn, which is the second messenger of EP1 receptors.

Subsequent blockade of EP1 receptors normalized both hyperalgesia and Ca^{2+} levels, suggesting that PGE_2 acts via EP1 receptors.[27] Reinold *et al.* performed several experiments with EP1-3 receptor-deficient mice, aiming to identify the mechanisms and the subtypes of EP-receptors involved in hyperalgesia. Intrathecal injection of PGE_2 caused mechanical and thermal hyperalgesia that were similar in $EP3^{-/-}$ and wild type (WT) mice. No hyperalgesia developed in $EP2^{-/-}$ mice. PGE_2-injection into the hind paw caused similar thermal sensitization in all mice, but mechanical sensitization was significantly reduced in $EP2^{-/-}$ mice. Local inflammation of the paw by zymosan A caused long-lasting hyperalgesia in WT and $EP3^{-/-}$ mice, while $EP2^{-/-}$ showed initial hyperalgesia that recovered within hours. Taken together, these findings suggest a crucial role of the EP2 receptor in spinal long-lasting hyperalgesia, and maybe a partial role of peripheral EP2 receptors in localized mechanical hyperalgesia.[11]

Johansson *et al.* investigated the contribution of EP1 receptors to inflammatory pain.[28] With the same laboratory setup as Reinold *et al.*, this time using $EP1^{-/-}$ mice, they showed significantly less hyperalgesia to heat stimuli after peripheral PGE_2 injection compared to WT or $EP2^{-/-}$ mice, suggesting that EP1 receptors are responsible for peripheral rather than spinal sensitization.[28]

Intrathecal injection of EP4 agonists in rats by Mebane *et al.* revealed significant touch-evoked allodynia, as well as mechanical and thermal hyperalgesia.[29] However, St-Jacques *et al.* later demonstrated a more peripheral EP4 effect localized to the dorsal root ganglion (DRG) neurons, suggesting that PGE_2 sensitizes DRG neurons and hereby induces COX-2/PGE_2/EP4 signaling trough EP4 externalization in DRG neurons.[30]

From bench to bedside: translating animal findings to human pain

The literature reviewed so far shows good evidence that spinal prostaglandins, particularly PGE_2, are involved in spinal nociception and sensitization. In summary, COX-1 and COX-2 are upregulated by painful stimuli, spinal PGE_2 causes pain and hyperalgesia, and these phenomena are attenuated by spinal application of COX-inhibitors or EP-antagonists. Unfortunately, the large amount of animal literature is paralleled by only a handful of human studies. Methodological limitations and ethical considerations are probably the main reasons for the limited data. Nevertheless, there is some evidence indicating similar effects in humans. Buvanendran *et al.* have investigated the relationship between postoperative pain in humans and prostaglandins in the cerebrospinal fluid. They demonstrated that IL-6 and PGE_2 increased markedly after total hip replacement. Moreover, the increase in PGE_2 was positively correlated to the intensity of postoperative pain, and preoperative administration of the COX-2 inhibitor rofecoxib was able to block this surgery-associated increase in PGE_2.[31]

Intrathecal NSAIDs in human experimental pain

Because differentiation between central and peripheral effects of NSAIDs is difficult in humans, most human experimental studies have used intrathecal (i.t.) administration of ketorolac, as this was the only preservative-free preparation with regulatory approval for intrathecal use.

Eisenach *et al.*[32] administered 2 mg of ketorolac i.t. in healthy volunteers who underwent experimental pain testing, using the skin sensitization model by topical capsaicin or the ultra-violet B (UV-B) burn model. Hypersensitivity was reduced after i.t. ketorolac only in the UV-B, but not in the capsaicin model. As the UV-B model is considered a model of inflammatory pain, these findings suggest NSAIDs exert central effects mainly in the presence of peripheral inflammation. Conversely, an intense C-fiber stimulation, as produced by the capsaicin model and possibly reflecting neuropathic pain hypersensitivity, does not seem to respond to centrally-administered NSAIDs.

In a study by Arendt-Nielsen *et al.*,[33] the COX-2 inhibitor etoricoxib significantly reduced both local and spreading sensitization, as well as temporal summation, in patients with knee osteoarthritis. Since temporal summation is likely a hypersensitivity phenomenon of dorsal horn neurons, the authors conclude that etoricoxib exerts at least parts of its effect in the central nervous

system. One could hypothesize that central effects of NSAIDs occur in the presence of a state of peripheral inflammation, which sensitizes dorsal horn neurons by continuous C-fiber nociceptive barrage. This might be the case in osteoarthritis or after UV-burn, in line with the aforementioned effects observed by Eisenach *et al.*[32]

Intrathecal NSAIDs in the surgical setting

Most studies investigating i.t. ketorolac in humans were performed in an orthopedic surgical setting, on patients undergoing spinal anesthesia. Compared to animal data, their results are somewhat ambiguous. Lauretti *et al.* added i.t. morphine, i.t. ketorolac, combined i.t. morphine and ketorolac or placebo to a routine spinal anesthesia (using 15 mg of bupivacaine) for knee arthroplasty in a four-arm double-blinded trial.[34] Their primary outcome measure was time to first analgesic rescue medication in the post-anesthesia care unit (PACU). Both i.t. morphine and i.t. ketorolac prolonged the time to first rescue medication to 7-8 hours compared to three hours in the placebo group. Co-administration of i.t. morphine and ketorolac resulted in significant potentiation of these effects and prolonged the time to first rescue medication to 16 hours. Furthermore, the combined i.t. morphine and ketorolac group had a significantly lower total analgesic consumption and did not require intravenous opioids at all. On the other hand, in a sample of 30 patients undergoing vaginal hysterectomy under spinal anesthesia with 15 mg bupivacaine and either 2 mg i.t. ketorolac or 2 mL saline, there was no difference in time to first i.v. morphine dose, postoperative pain scores or total amount of morphine consumed in the PACU.[35]

These findings are similar to those by Wang *et al.*,[36] who tested i.t. ketorolac *vs*. placebo as an adjunct to spinal anesthesia for hip arthroplasty. Neither post-operative opioid use nor pain scores differed between the two groups. However, the study had to be terminated early because the only ketorolac preparation approved for intrathecal use was no longer manufactured. Malmberg and Yaksh[2] had shown initially that spinal upregulation of COX and prostaglandins is mediated by continuous afferent C-fiber nociceptive input. As spinal anesthesia blocks this continuous nociceptive input, it might not be a suitable model for detecting central effects of NSAIDs.

Intrathecal NSAIDs in human chronic pain

The first attempt to use spinal NSAIDs in chronic pain dates 1987, when Pellerin *et al.* injected acetylsalicylate epidurally in advanced cancer patients. They reported significant and long-lasting analgesia in a series of 60 patients.[37] Only decades later, Eisenach *et al.* examined a group of chronic pain patients receiving intrathecal morphine via an implanted pump.[35] Their usual drug was removed from the pump and replaced by ketorolac or placebo in a double-blinded fashion. They reported a significant analgesic effect, which, however, did not differ between placebo and ketorolac. The amount of PGE_2 in the CSF samples was reduced by ketorolac, but only in patients who had high baseline PGE_2 concentrations. In patients with normal baseline PGE_2, its concentration was not affected by ketorolac. Interestingly, only those patients with high baseline PGE_2 and concomitant reduction by ketorolac reported a strong analgesic effect, partly in line with animal data.

Conclusions

The central effects of NSAIDs are supported by a large body of evidence in animals. The central effects in inflammatory pain are robustly explained, whereby spinal inflammation-induced COX-2 expression and local PGE_2 concentration increases in the dorsal horn are linked to a decreased efficacy of inhibitory glycinergic interneurons. The importance of glycine in human pain modulation could be recently confirmed.[38] Neuropathic pain seems to be linked to mechanisms largely independent of the COX-2-PGE_2-EP2 pathway, as demonstrated in multiple animal models.[39]

Methodological restrictions in humans, such as risks associated with repeated dural punctures, difficulty to study inhibitory postsynaptic currents and inflammatory mediators the same way as in animals, as well as ethical considerations,

make it difficult to selectively investigate central effects of NSAIDs. Human research must rely on surrogate markers and assess indirect effects. Results are therefore less clear-cut as compared to animal studies. Future research might address these questions using experimental settings other than spinal anesthesia with intrathecal NSAIDs. General anesthesia or measures of spinal hyperexcitability (*e.g*. nociceptive reflexes or temporal summation) might provide more insight. Translational research has nevertheless produced significant results since the first description of NSAID's spinal effects by Malmberg *et al.*[2] and has increased our knowledge on the central prostaglandin E_2 signaling pathway in inflammatory pain. Moreover, specific EP-antagonists might offer a novel approach to pain treatment, although their use is currently confined to the laboratory setting.

Key messages

• Animal data revealed significant increases in spinal cord PGE_2 levels in peripheral inflammation as well as in surgical and neuropathic pain models.

• PGE_2-induced central sensitization seems to be mediated by a COX-2-PGE_2 response to proinflammatory cytokines, resulting in phosphorylation and inhibition of the glycine receptor α3 in the superficial spinal cord dorsal horn.

• In humans spinal PGE_2 build-up is positively correlated to the intensity of postoperative pain, whereby preoperative administration of the COX-2 inhibitors blocks this surgery-associated increase in PGE_2.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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